A Comparative Study of Fentanyl and Clonidine on Hemodynamic Response to Pneumoperitoneum in Laparoscopic Cholecystectomy

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Abstract- Aims **-** To compare the efficacy of clonidine and fentanyl for attenution of hemodynamic response to pneumoperitoneum.
Method – Sixty patient of ASA grade I and II were divided into two groups:
Group A: patients receiving 2 mcg/kg fentanyl, as premedication
Group B: patients receiving 2 mcg/kg clonidine, as premedication
Patients were given general anaesthesia and hemodynamic response to pneumoperitonium was noted and patients were monitored for postoperative analgesia and sedation. Data obtained were subjected to stastical analysis.
Result -SBP in subjects of group B remains significantly lowered during the different phases of treatment as compared to group A ($p<0.01$) from at intubation to till end except 5 min after intubation. The mean DBP in subjects of group B remains lowered during different phases of treatment as compared to group A. HR in subjects of group B lowered significantly ($p<0.01$) from at after 5 min to till end as compared to group A.Pain in subjects of group B (4.60 ± 1.43) just after surgery was found to be significantly ($p<0.01$) lower as compared to group A (6.00 ± 1.03) while in other periods it did not differed significantly ($p>0.05$) between the two groups i.e. remains statistically the same.Just after surgery, the mean sedation in subjects of group B (3.50 ± 0.76) were comparatively high as compared to group A (1.40 ± 0.50)**.**
Conclusion - Clonidine is better than fentanyl for attenuation of haemodynamic response to pneumoperitoneum during laproscopic cholecystectomy. It has more analgesic action than fentanyl and provides more sedation than fentanyl.Clonidine does not prolong extubation time significantly.

Index terms- clonidine, fentanyl, pneumoperiotnium, laparoscopic cholecystectomy, opioid, alpha agonist, premedication, general anaesthesia

1 INTRODUCTION

Laparoscopic cholecystectomy is a common surgery now days. Pneumoperitoneum is created using CO_2 insufflations. Creation of pneumoperitoneum is associated with sympathetic stimulation and stress response which results in hemodynamic changes as tachycardia and hypertension. The α_2 agonists have been shown to following properties that are of potential benefit in premedication [1]:

- ●Sedation
- ●Anxiolysis
- ●Drying of secretions
- ●Reduction in requirement of anaesthetic agents
- ●Improved cardiovascular stability in perioperative period
- ●Analgesia
- ●Decreased post-operative nausea, vomiting and shivering

Clonidine is the prototype α-2 agonist that has been extensively studied in animals and humans. It is a partial agonist with a ratio of 200:1 (α2: α1). A major effect of clonidine is decreased sympathetic nervous system activity [2]. This is indicated by decreased blood levels of epinephrine and norepinephrine [3],[4]. Although sympathetic activity is reduced, baroreflex responses are maintained in normotensive humans [5]. Many investigators have reported better hemodynamic control, particularly on endotracheal intubation [1], and a stable cardiovascular course in hypertensive patients in patients for abdominal surgery [5], ophthalmic surgery [7] and craniotomies [8]. Clonidine reduces post operative shivering [9]. Clonidine also reduces the incidence of post-operative vomiting [10].

Opioid are used in general anaesthesia to blunt the hemodynamic response to intubation and surgical stress but they are associated with nausea, vomiting and respiratory depression.

We compared these two classes of drugs to attenuate the hemodynamic response to pneumoperitoneum.

2 MATERIALS AND METHOD

Study design: Randomized, prospective, double blind, case control study

After getting approval from the institutional ethical committee, an informed consent was taken from the patient and their attendant. The study was conducted on 60 admitted patients of a tertiary care hospital of either sex, aged between 20 to 50 years belonging to ASA physical status I or II undergoing laparoscopic cholecystectomy in between January, 2011 and December, 2012. Patients were divided in two groups using a computer generated random number table:

Group A: patients receiving 2 mcg/kg fentanyl
Group B: patients receiving 2 mcg/kg clonidine

Data collection was done by investigator blinded to group allocation.

On arrival to operating room, standard monitors including non invasive blood pressure monitoring, pulse oximetry and electrocardiogram were applied to all patients. An 18 gauge intravenous line was secured and 500 ml of lactated ringer solution was given as preloading. Patients were premedicated with inj. ondensetron 4 mg iv and inj. glycopyrrolate 0.2 mg iv. Patients were given 2mcg/kg fentanyl in group A and 2 mcg/kg clonidine in group B. The study drugs in each group was diluted in 10 ml of saline and infused over 5 minutes. Patients were induced with 2mg/kg propofol and intubated with 0.1mg/kg of vecuronium. Anaesthesia was maintained with N_2O (60%), O_2 (40%) and halothane 0.5 MAC. Relaxation was achieved with intermittent doses of vecuronium. After completion of surgery, neuromuscular blockade was reversed with neostigmine and glycopyrrolate (0.05 mg/kg and 0.01mg/kg). Vitals were monitored throughout the procedure. Ramsay sedation score and VAS score was noted after extubation. The *Ramsay sedation scale* is used to assess the level of sedation of a hospitalized patient. It was described by Michael A. E. Ramsay.

The scale, from 1 to 6, describes a patient as follows:

1. anxious and agitated or restless, or both
2. co-operative, oriented, and calm
3. responsive to commands only
4. exhibiting brisk response to light glabellar tap or loud auditory stimulus
5. exhibiting a sluggish response to light glabellar tap or loud auditory stimulus
6. unresponsive

Continuous data were summarized as Mean ± SD while discrete (categorical) in %. The primary outcome measures (heart rate, systolic BP, diastolic BP and mean BP) of three groups over the periods (time) were compared by repeated measures two factor (periods and groups) analysis of variance (ANOVA) using general linear models (GLM) and the significance of mean difference between the groups was done by Bonferroni multiple contrast test after ascertaining the homogeneity of variance by Levene's test. Groups were also compared by one way ANOVA followed by Tukey's post hoc test. The discrete (categorical) variables were compared by chi-square (χ^2) test. A two-sided (α=2) $p<0.05$ was considered statistically significant. All analyses were performed on STATISTICA (window version 6.0).

3 RESULTS

Comparing the characteristics of three groups; the mean age and percentage of gender, weight and ASA physical status of two groups were found to be statistically the same i.e. did not differ significantly ($p>0.05$). In other words, subjects of three groups were age, sex and weight matched. Further, the groups of patients were also matched with diagnosis, operation done and duration of surgery. Thus, the age, gender, diagnosis, mode and duration of operation may not influence the outcome measures.

The mean duration of surgery of all two groups were found to be the same ($F=0.0381$, $p=0.9626$) i.e. did not differed significantly. The duration of surgery in group A and group B ranged from 60-120 min and 45-120 min respectively with mean (± SD) 88.75 ± 17.16 min and 87.75 ± 16.93 min respectively.

The SBP in subjects of two groups during different phases of treatments showed that the mean SBP in subjects of group B remains significantly lowered during the different phases of treatment as compared to group A ($p<0.01$) from at intubation to till end except 5 min after intubation.

The mean DBP in subjects of group B remains lowered during different phases of treatment as compared to group A. On comparing the mean DBP in subjects of two groups during different phases of treatments, the DBP in subjects of group B were found to be significantly ($p<0.01$) lower from at induction to till end as compared to group A except 1 min after intubation.

On comparing the mean MAP in subjects of two groups during different phases of treatments, the MAP in subjects of both group B lowered significantly ($p<0.01$) lower from at intubation to till end as compared to group A.

On comparing the mean HR in subjects of two groups during different phases of treatments, the HR in subjects of group B lowered significantly ($p<0.01$) from at after 5 min to till end as compared to group A.

Pain in subjects of group B (4.60 ± 1.43) just after surgery was found to be significantly ($p<0.01$) lower as compared to group A (6.00 ± 1.03) while in other periods it did not differed significantly ($p>0.05$) between the two groups i.e. remains statistically the same.

Just after surgery, the mean sedation in subjects of group B (3.50 ± 0.76) were comparatively high as compared to group A (1.40 ± 0.50). On comparing sedation in subjects of two groups, the sedation in subjects of group B at just after surgery, 6 hr after surgery and 12 hr after surgery was found to be significantly higher ($p<0.05$ or $p<0.01$) as compared to group A. However, the mean Sedation in both groups at 18 hr after surgery and after 24 hr surgery remains the same i.e. did not differed significantly ($p>0.05$).

The time of eye opening in group A and group B ranged from 2.00-4.00 min and 3.00-5.30 min respectively with mean (± SD) 2.83 ± 0.67 min and 4.35 ± 0.68 min respectively. The mean time of eye opening was slightly higher in group B as compared to group A.

The time to follow verbal commands in group A group B ranged from 2.15-4.35 min and 3.30-6.00 min respectively with mean (± SD) 3.32 ± 0.70 min and 4.84 ± 0.68 min, respectively. The mean time to follow verbal commands was comparatively higher in group B as compared to group A.

On comparing, the mean time to extubate in group B (6 min) was found to be significantly ($p<0.01$) higher than group A. The time to extubate in group A and group B ranged from 3.00-5.00 min and 4.00-6.30 min respectively with mean (± SD) 3.87 ± 0.62 min and 5.25 ± 0.73 min, respectively.

4 DISCUSSION

Laparoscopic surgeries are becoming popular due to multiple benefits associated with it like less tissue damage, small skin incision and better aesthesis, less postoperative pain and early discharge from the hospital. But creation of pneumoperitoneum is associated with sympathetic stimulation and various other adverse physiological effects. Various pharmacological agents have been tried to attenuate these responses like opioid, beta blocker, α 2 agonists, nitroglycerine, etc. We have compared the two most commonly used agents for this purpose. Besides attenuating the autonomic response to pneumoperitoneum, these two agents have potent analgesic properties which are advantageous during perioperative period. Using these agents as premedication drugs, we tried to compare their effects on hemodynamic fluctuations during laparoscopic cholecystectomy.

By comparing the blood pressure and heart rate in the two groups, we can see that the heart rate and blood pressure is significantly lower in clonidine group as compared to fentanyl group. Thus, this study showed that hemodynamic response to laryngoscopy and pneumoperitoneum is blunted more effectively by clonidine than fentanyl. Furthermore, the hemodynamic variables showed less fluctuation in clonidine group showing that clonidine provides hemodynamic stability throughout the procedure. The rise in blood pressure and heart rate due to intubation and extubation was also suppressed by clonidine more efficiently than fentanyl.

The time to extubation was significantly higher in clonidine group on stastical analysis but practically it is not significant as the difference between the times of extubation in two groups was only 2 minutes (5.25 ± 0.73 min Vs 3.87 ± 0.62 min). Thus, we can safely conclude that practically, time of extubation is not prolonged by clonidine.

Pain scores were lower with clonidine as compared to fentanyl in immediate postoperative period suggesting that clonidine provides better analgesia due to their longer duration of action as compared to fentanyl. However, pain scores after 6 hrs. of surgery were same in both groups which represents the normal duration of action of clonidine. This ultimately reduces the supplemental analgesic requirement and allows rapid postoperative recovery.

Sedation scores were higher in patients premedicated with clonidine as compared to fentanyl up to 12 hrs after surgery, so the patient were more comfortable and calm after surgery with the use of clonidine. Patient premedicated with clonidine were easily arousable and have less anxiety after extubation. This may also be due to better analgesia provided by clonidine. None of the patient in both groups required any intervention for postoperative respiratory depression. The sedation scores at and after 18 hrs. in both groups were comparable and this may represent the maximum duration of sedative action of clonidine.

Thus, the result from our study showed that clonidine is a better agent to attenuate the hemodynamic response to pneumoperiotoneum during laparoscopic cholecystectomy and it also blunts the sympathetic response to laryngoscopy and extubation better than fentanyl. Clonidin also provides better postoperative analgesia and sedation as compared to fentanyl and patient is more relaxed and calm without any respiratory depression.

5 CONCLUSION

From our study, we conclude that clonidine is better than fentanyl for attenuation of haemodynamic response to pneumoperitoneum during laproscopic cholecystectomy. It has more analgesic action than fentanyl and provides more sedation than fentanyl.Clonidine does not prolong extubation time significantly. So, 2 mcg/kg clonidine is more effective in haemodynamic stability during laproscopic cholecystectomy than 2 mcg/kg fentanyl without any adverse effects.

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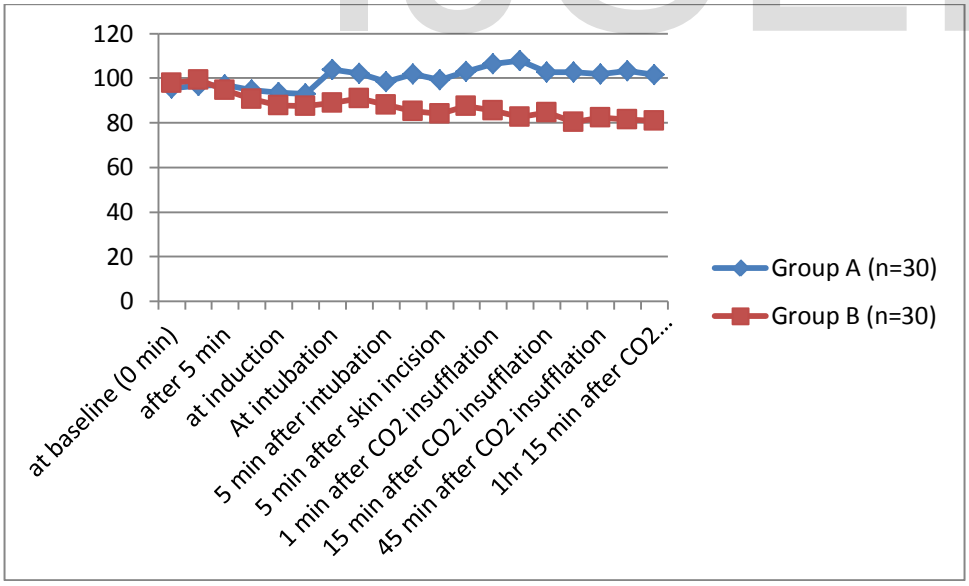

Figure 1: MAP in subjects of two groups during different phases of treatments

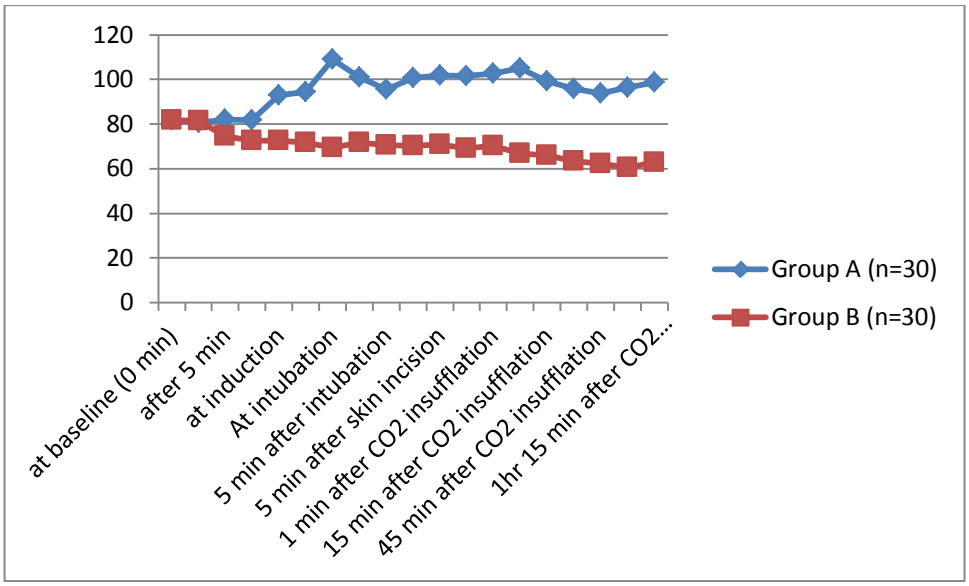

Figure 2: HR in subjects of two groups during different phases of treatments

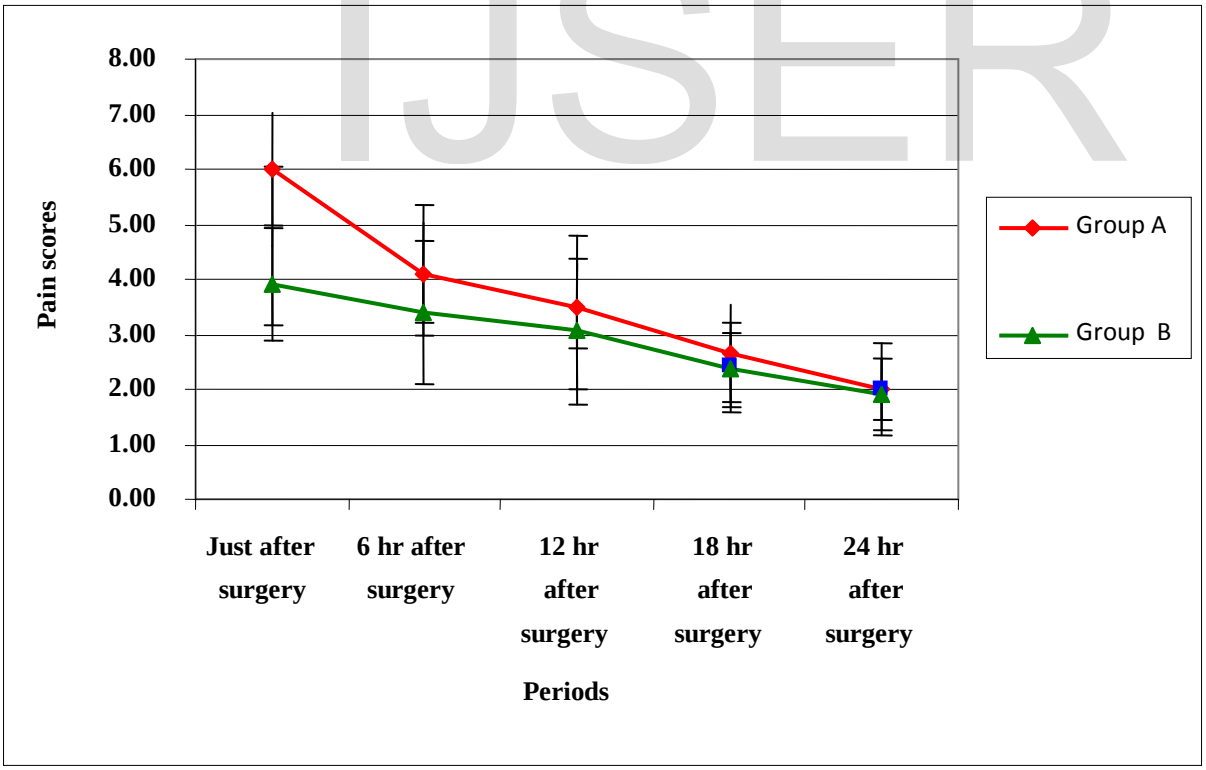

Figure 3: Pain after surgery in subjects of two groups

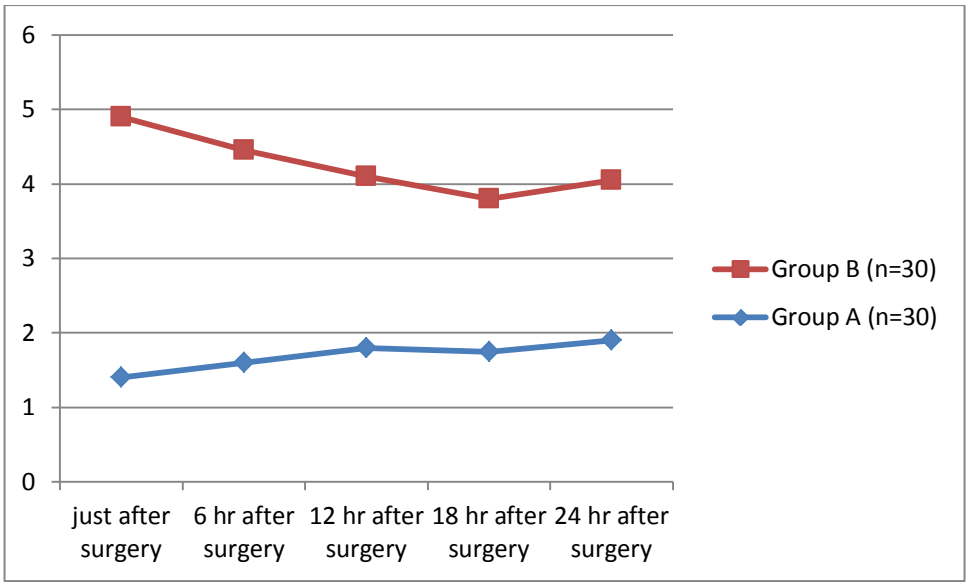

Figure 4: Sedation after surgery in subjects of two groups

Characteristics	Group A (n=30)	Group B (n=30)	P Value
Sex (male/female)	6/24	7/23	0.7408
Age (yrs)	33.95 ± 6.67	34.30 ± 7.95	0.9913
Weight (kg)	57.20 ± 8.57	58.70 ± 8.19	0.4431
SBP (mmHg)	121.40 ± 10.85	126.95 ± 10.67	0.1216
DBP (mmHg)	82.55 ± 7.10	83.20 ± 6.35	0.9652
MAP (mmHg)	95.50 ± 7.86	97.78 ± 7.03	0.0818
HR (beat/min)	81.65 ± 8.36	81.75 ± 4.25	0.4993

Table 1: Baseline characteristics of the patients in the two groups

Characteristics	Group A (n=30)	Group B (n=30)	P Value
Duration of surgery (min)	88.75 ±	87.75 ±	0.9626

	17.16	16.93	
Time of eye opening (min)	2.83 ± 0.67	4.35 ± 0.68	p<0.01
Time to follow verbal commands (min)	3.32 ± 0.70	4.84 ± 0.68	p<0.01
Time to extubate (min)	3.87 ± 0.62	5.25 ± 0.73	p<0.01

Table 2: Secondary outcome variables in two groups